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(54) Biodegradable polymer composition

Biologisch abbaubare Polymerzusammensetzung
Compositions biodégradables de polymère

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DescriptionBackground of the Invention

Polymeric implants are useful as delivery systems and/or as mechanical barriers. Implants such as pre-formed membranes or films have been described. However, many of these implants have limited properties and produce inferior results either as mechanical barriers or delivery systems.

Several implant techniques have been used in medical and dental applications. One application of interest is the use of implants in treatment of periodontal disease. Surgery alone does not result in restoration of lost periodontium. Successful periodontal restoration is known to occur if periodontal ligament cells are allowed to colonize root surfaces preferentially over gingival epithelial cells, gingival fibroblasts or osteoblasts. Microporous membranes, such as the Millipore® filter and GORE-TEX® membranes, have been used for periodontal tissue regeneration. Typically, the periodontal flap is cut, and the membrane is surgically inserted to cover the surface of the tooth root and to physically occlude epithelial cells from apically migrating along the root surface.

Those membranes, however, have several drawbacks. Besides variable results, a second surgical entry is needed to remove the membrane after tissue regeneration has been achieved because the membranes are not biodegradable. There is also a higher incidence of infection in connection with their use.

To preclude surgical removal of the implant, membranes made of bioabsorbable material, such as microfibrillar collagen, polylactic acid, and polygalactin (Vicryl®) mesh have been used. Results have been variable, and the therapeutic effect of these membranes has been unpredictable. In addition, fitting and positioning these membranes to the implant site is time-consuming and cumbersome. Also, the degradation time of membranes composed of collagen has been variable, and the risk of adverse immunological reaction to this foreign protein material in the body presents a major concern.

Therefore, an object of the invention is to provide a composition comprising a biodegradable or bioerodible polymer suitable for forming an *in-situ* solid implant in an animal including a human. Another object is the development of an implant that will eliminate the need for its surgical removal after its purpose has been achieved. Another object is to provide a composition which may be administered to an implant site in liquid form and which is capable of solidifying *in-situ* to form an implant. A further object of the invention is to provide a biodegradable implant which may be used to enhance connective cell or tissue growth and deter growth of epithelial cells and tissue into the core of the implant. Yet another object is to provide an implant which is capable of delivery of a drug or other medicament over

a desired period of time. A further object is to provide an implant for providing controlled release delivery of at least one biologically-active agent for stimulation and/or enhancement of physiological or biological activity in an animal.

Summary of the Invention

These and other goals are achieved by the present invention which is directed to a composition suitable for forming an *in situ* solid or gelatinous biodegradable or bioerodible microporous matrix upon contact with aqueous or body fluid, the matrix being a core surrounded by a skin, the core containing pores of diameter from 10 to 1000 microns, and the skin containing pores of smaller diameters than those of the core pores. The matrix may be used to deliver biologically-active substances and/or for selective enhancement of cell growth and tissue regeneration in animals.

The composition is a formulation of a biocompatible and biodegradable or bioerodible thermoplastic or thermoset polymer or copolymer which is insoluble in aqueous or body fluids. The composition may include a separate pore-forming agent which is capable of generating additional pores within the polymer matrix. When a biologically-active agent is to be released by the matrix, the agent is dissolved in the composition to form a homogenous solution or dispersed in the composition to form a suspension.

The invention provides a composition for use as an *in-situ* forming microporous biodegradable implant in a body which can be used for tissue, nerve, periodontium or bone regeneration.

The invention also provides a use of the composition for the manufacture of a preparation for *in-situ* forming of a microporous biodegradable implant in a body.

Thermoplastic polymer compositions

According to a first embodiment of the invention, the composition is a liquid formulation of a thermoplastic polymer and a pharmaceutically acceptable organic solvent. The composition is administered as a liquid to an implant site, whereupon the solvent diffuses or dissipates into the surrounding aqueous tissue fluids. The thermoplastic polymer is not soluble in these aqueous fluids so that it coagulates or solidifies to form a microporous solid or gelatinous matrix. The matrix has a two-layered pore structure composed of a core portion and an outer surface layer or skin, and the core contains pores of diameters from 10 to 1000 microns, and the skin contains pores of smaller diameters than those of the core pores. The polymer matrix is suitable for use as an *in situ* formed implant in an animal, including humans and other mammals. The composition may be administered to tissue, to a surgical incision, or to a void space in tissue such as a periodontal pocket, and the like.

Thermoset polymer compositions

According to a second embodiment of the invention, the composition is a liquid formulation of a thermoset prepolymer or copolymer, preferably an acrylic ester-terminated biodegradable prepolymer, which is capable of cross-linking *in situ* to form a polymeric or copolymeric solid or gelatinous matrix. The composition preferably is a neat liquid but may include a pharmaceutically acceptable organic solvent that is miscible with water and body fluids.

When the thermoset polymer composition is cross-linked *in situ*, the resulting matrix is rendered microporous by one of several means. Use of a small but suitable amount of organic solvent will produce pores as described above for the thermoplastic polymer. The prepolymer ingredients may release a pore-forming moiety such as carbon dioxide and the like, or a separate pore-forming agent may be included. The pore-forming agent may be any suitable organic or inorganic substance which is soluble or substantially miscible in water and tissue fluids, and substantially miscible or dispersible in the thermoset polymer composition.

The thermosetting polymer composition may include a curing agent, such as a catalyst, which is capable of enhancing the cross-linking reaction of prepolymers. The curing agent is biocompatible. Preferred catalysts include benzoyl peroxide and azobisisobutyronitrile.

Porosity of the polymer matrices

Several factors influence the size, or diameter, of the pores formed in the polymer matrix of the implant. In the polymer matrices formed from the thermoplastic polymer composition and from the thermoset polymer composition containing solvent or pore-forming moiety, the action of the solvent (or pore-forming moiety), as it diffuses out of the coagulating or solidifying polymer matrix and into the surrounding tissue fluids, generates pores in the matrix and produces a two-component structure. The outer component is a surface skin which surrounds the inner component or core. The core contains pores of diameter from about 10 to 1000 μ while the skin is functionally non-porous in comparison with the core. In fact, the skin has pores which are significantly smaller in diameter than those of the core.

The addition of a pore-forming agent to the thermoplastic polymer composition and the use of a pore-forming agent as part of the thermoset polymer composition can produce a matrix having about the same diameter pores throughout the core and skin. The size and/or quantity of a pore-forming agent included in the polymer matrix, and the distribution of the pore-forming agent within the polymer matrix, among other factors, may also influence pore size and porosity of the polymer matrix.

Where the implant is employed for the purpose of

tissue regeneration, as for example, to promote guided tissue regeneration of periodontal tissue, it is preferred that the diameter of the pores in the matrix be effective to deter growth of epithelial cells into the polymer matrix of the implant, and enhance growth of connective tissue cells into the matrix. It is further preferred that the size of the pores and porosity of the matrix of the implant facilitate diffusion of nutrients and other growth-promoting substances such as growth factors, to cells which have grown into the matrix. Preferably, the size of the pores in the polymer matrix is about 3-500 microns, more preferably about 3-200 microns, and most preferably about 75-150 microns.

It is further preferred that the degree of porosity of the matrix provides an implant which is capable of substantially maintaining structural integrity for the desired period of time without breakage or fracturing during use.

Biologically-active Agent

The composition may further contain at least one biologically-active agent which is capable of providing a biological, physiological or therapeutic effect in an animal. For example it may enhance cell growth and tissue regeneration, act for birth control, cause nerve stimulation or bone growth. The agent may also stimulate other desired biological or physiological activity within the animal. Accordingly, the invention provides an *in situ* formed implant capable of functioning as a delivery system of drugs, medicaments and other biologically-active agents to tissues adjacent to or distant from the implant site. The biologically-active agent is preferably incorporated into the polymer matrix, and subsequently released into surrounding tissue fluids and to the pertinent body tissue or organ.

Administration of the Composition

The composition may be administered to the implant site by any suitable method for applying a liquid, as for example, by means of a syringe, needle, cannula, catheter, pressure applicator, and the like. In one embodiment, the composition may be administered by means of a syringe directly into integral tissue or into a void or hole such as a periodontal pocket or surgical incision, wherein the mixture *in situ* forms a solid implant conforming to the shape or the contour of the site. Advantageously, the composition of the invention is useful in overcoming placement difficulties inherent with solid forms of implants.

The invention further provides a use of the composition for the manufacture of a preparation for altering a biological or physiological activity in an animal. This involves administering to an animal, one of the foregoing compositions in an amount effective to form a solid microporous matrix implant in the animal. The matrix, optionally containing at least one biologically-active agent, is capable of enhancing cell growth and/or tissue

formation such as bone or nerve formation, or altering a biological or physiological activity in an animal such as reproductive function and the like.

Detailed Description of the Invention

The composition of the invention may be used to provide a biodegradable or bioerodible microporous in situ formed implant in animals. The composition is composed of either a thermoplastic polymer or copolymer in combination with a suitable solvent, or a thermosetting polymer or copolymer containing or combined with a pore-forming means. The polymers or copolymers are insoluble in water and body fluids, biocompatible, and biodegradable and/or bioerodible within the body of an animal. The compositions are administered as a liquid to tissue wherein the implant is formed in situ. The composition is biocompatible and the polymer matrix does not cause substantial tissue irritation or necrosis at the implant site. The implant has a variety of uses, as for example, for enhancing cell growth and tissue regeneration, and delivery of biologically-active agents such as drugs and medicaments.

Thermoplastic polymer composition

Thermoplastic polymers useful in the composition of the invention include pharmaceutically compatible polymers that are bioerodible by cellular action, are biodegradable by action of non-living body fluid components, soften when exposed to heat but return to the original state when cooled and are capable of substantially dissolving or dispersing in a water-miscible carrier or solvent to form a solution or dispersion. Upon contact with an aqueous fluid and the dissipation of the solvent component, the thermoplastic polymers are capable of coagulating or solidifying to form a solid or gelatinous matrix suitable for use as an implant in an animal.

The kinds of thermoplastic polymers suitable for the present composition generally include any having the foregoing characteristics. Examples are polylactides, polyglycolides, polycaprolactones, polyanhydrides, polyamides, polyurethanes, polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates, polyphosphazenes, polyhydroxybutyrates, polyhydroxyvalerates, polyalkylene oxalates, polyalkylene succinates, poly(malic acid), poly(amino acids), poly(methyl vinyl ether), poly(maleic anhydride), chitin, chitosan, and copolymers, terpolymers, or combinations or mixtures therein. Polylactides, polycaprolactones, polyglycolides and copolymers thereof are highly preferred thermoplastic polymers.

The thermoplastic polymer is combined with a suitable organic solvent to form a solution. The solubility or miscibility or dispersability of a polymer in a particular solvent will vary according to factors such as crystallinity, hydrophilicity, capacity for hydrogen-bonding and

molecular weight of the polymer. Consequently, the molecular weight and the concentration of the polymer in the solvent are adjusted to achieve desired miscibility. Highly preferred thermoplastic polymers are those which have a low degree of crystallization, a low degree of hydrogen-bonding, low solubility in water, and high solubility in organic solvents.

Thermoset polymer compositions

The composition of the invention may as well be a liquid formulation of a thermosetting oligomeric pre-polymer or copolymer which is capable of cross-linking or hardening to provide a microporous gelatinous or solid matrix suitable for use as an implant in an animal, including a human. The thermosetting pre-polymers and resulting cross-linked polymers and copolymers are biocompatible, and biodegradable and/or bioerodible.

The pre-polymers are preferably low molecular weight polymers or oligomers having end functional groups that are reactive with acryloyl chloride to produce acrylic ester-terminated pre-polymers. Acrylic pre-polymers for use in the compositions may be synthesized according to a variety of methods including, but not limited to, reaction of a carboxylic acid, such as acrylic or methacrylic acid, with an alcohol; reaction of a carboxylic acid ester, such as methyl acrylate or methyl methacrylate, with an alcohol by transesterification; and reaction of an isocyanatoalkyl acrylate, such as isocyanatoethyl methacrylate, with an alcohol.

The thermosetting prepolymers are also short chain polyol derivatives of the thermoplastic polymers described herein. The polyol terminated derivatives are converted to acrylic ester terminated prepolymers by any suitable method. Examples are short chain polyol derivatives of polylactides, polyglycolides, polycaprolactones, polyanhydrides, polyamides, polyurethanes, polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates, polyphosphazenes, polyhydroxybutyrates, polyhydroxyvalerates, polyalkylene oxalates, polyalkylene succinates, poly(malic acid), poly(amino acids), poly(methyl vinyl ether), poly(maleic anhydride), chitin, chitosan, and copolymers, terpolymers, or combinations or mixtures therein.

A preferred polymer matrix and implant prepared with thermosetting prepolymers is composed of poly(DL-lactide-co-caprolactone) (DL-PLC). To prepare the DL-PLC polymer matrix, DL-lactide or L-lactide and ε-caprolactone are co-polymerized in the presence of a multifunctional polyol initiator and a curing agent to produce hydroxy-terminated PLC prepolymers. This polyol-terminated pre-polymer is then converted to an acrylic ester-terminated pre-polymer by any suitable method, as for example, by acylation of the alcohol terminus with acryloyl chloride by means of, for example, a Schotten-Baumann technique (reaction of acyl halide with alcohol).

Optionally, a curing agent, such as a catalyst, may be added to the acrylic pre-polymer mixture to enhance cross-linking of the pre-polymers and the subsequent coagulation or solidification of the resulting polymer to form a matrix. For example, the acrylic pre-polymer, in an amount of about 5 grams, may be added to a solution of benzoyl peroxide (BP) in about 1 ml of CH_2Cl_2 . Optionally, other acrylic monomers may be added to the acrylic pre-polymer mixture before adding the curing agent. The acrylic pre-polymer mixture may be cured in air at room temperature, or in a preheated vacuum oven.

Preferred catalysts for the preparation of the PLC prepolymers are basic or neutral ester-interchange (transesterification) catalysts, as for example, metallic esters of carboxylic acids containing up to 18 carbon atoms, formic, acetic, lauric, stearic, and benzoic acid. Preferred catalysts include, for example, stannous octoate and stannous chloride.

A multi-functional polyol chain initiator may be included in the thermosetting polymer compositions to vary the molecular weight and composition of the polymer. For example, a bifunctional chain initiator such as ethylene glycol, may be included to produce a bifunctional polymer, or a trifunctional initiator, such as trimethylolpropane, may be used to produce a trifunctional polymer. Further, the molecular weight of the polymer or co-polymer may be varied according to the concentration of the chain initiator in the composition. For example, a high concentration of a bifunctional chain initiator may make available an initiator molecule for each polymer chain, while a low concentration may contain one initiator molecule for every two polymer chains.

Following the addition of the curing agent, the pre-polymer polymer mixture preferably remains in liquid form for a period of time effective to allow administration of the composition to the implant site. Thereafter, the cross-linking reaction preferably continues until a solid or gelatinous polymer matrix is produced. Accordingly, the pre-polymer mixture cures, or solidifies, *in situ* to form a polymer matrix which is capable of biodegradation and/or bioabsorption over time.

The thermoset polymer composition contains one or more materials to form the microporous matrix. The polymer itself can contain moieties that are released as volatile substances during cross-linking to cause pore formation. Alternatively, the composition can contain a minimum amount of suitable, biocompatible organic solvent as described below, or can contain a separate pore-forming agent as discussed below. The thermoset polymers containing releaseable moieties are known in the art.

Solvents

Solvents suitable for the thermoplastic polymer composition are those which are biocompatible, prefer-

ably pharmaceutically acceptable, miscible with the polymer component, miscible, soluble or dispersible in aqueous or body fluid, and capable of diffusing into tissue fluids surrounding the implant site. Preferably, the solvent has a Hildebrand (HLB) solubility ratio of from about $(9\text{cal}/\text{cm}^3)^{1/2}$ 18 ($\text{J}/\text{cm}^3\right)^{1/2}$ to $(13\text{cal}/\text{cm}^3)^{1/2}$ 26 ($\text{J}/\text{cm}^3\right)^{1/2}$. The degree of polarity of the solvent should be effective to provide at least about 10% solubility in water, and to dissolve or disperse the polymer component into solution.

According to the invention, the composition is administered to the implant site in liquid form, whereupon the solvent diffuses into the adjacent tissue fluids. Upon contact with the surrounding aqueous fluids, the polymer moiety coagulates or solidifies to form a solid or gelatinous matrix fitting the usually irregular shape of the incision or void of the implant site. Preferably, the solvent quickly diffuses into the surrounding tissue fluids to enhance formation of the polymer matrix following administration of the composition to the implant site. Preferably, the polymer matrix is capable of adhering to the adjacent tissue by mechanical forces to at least partially bond or attach the implant to the adjacent tissue, and/or mechanically bond two tissues together. The concentration of polymer in solvent for the composition will generally accomplish rapid and effective dissipation of the solvent and coagulation of the polymer. This concentration may range from 0.01g of polymer per ml of solvent to a saturated concentration, preferably from 0.1g per ml to saturation.

Solvents which may be used in the thermoplastic polymer composition of the invention include, for example, N-methyl-2-pyrrolidone, 2-pyrrolidone, C_2 to C_6 alkanols, propylene glycol, acetone, alkyl esters such as methyl acetate, ethyl acetate, ethyl lactate, alkyl ketones such as methyl ethyl ketone, dialkylamides such as dimethylformamide, dimethyl sulfoxide, dimethyl sulfone, tetrahydrofuran, cyclic alkyl amides such as caprolactam, decylmethylsulfoxide, oleic acid, propylene carbonate, aromatic amides such as N,N-diethyl-m-toluamide, and 1-dodecylazacycloheptan-2-one. Preferred solvents according to the invention include N-methyl-2-pyrrolidone, 2-pyrrolidone, dimethyl sulfoxide, acetone, and propylene carbonate.

A mixture of solvents may be used to increase the coagulation rate of polymers which exhibit a slow coagulation or setting rate. For example, the polymer may be combined with a coagulant-promoting solvent system composed of a mixture of a good solvent and a poorer solvent or a non-solvent for the polymer component. It is preferred that the solvent mixture contain an effective amount of the two solvents such that the polymer will remain soluble in the mixture but coagulate upon dissipation or diffusion of the solvents into surrounding tissue fluids at the implant site.

The same solvents can also be combined with the thermoset polymer composition. In this variation, the solvent does not form the liquid character of the compo-

sition. The prepolymer itself is liquid. Instead the solvent acts to produce the two component porous matrix discussed below. The solvent concentration is at a minimum for such purpose and is preferably inert toward the cross-linking reaction. The solvent diffuses as the prepolymer hardens to form the solid implant matrix. The organic solvent is included in the thermosetting polymer composition in an amount suitable to form pores but not high enough to substantially dilute the pre-polymer ingredient to a condition where it only lightly cross-links.

Pore-formation and porosity

Upon contact with an aqueous body fluid or water, the thermoplastic polymer composition coagulates or solidifies to form a microporous gelatinous or solid matrix. Similarly, the thermoset polymer composition hardens to form a microporous solid matrix. In either variation, pores may be formed within the matrix by several means. Dissipation, dispersement or diffusion of the solvent or released moiety (thermoset polymer) out of the solidifying polymer matrix or hardening polymer matrix (thermoset polymer) and into the adjacent tissue fluids may generate pores, including pore channels, in the polymer matrix.

Diffusion of the solvent or released moiety produces a thermoplastic or thermoset polymer matrix having a two component structure, that is, an inner core portion or layer, and an outer surface portion or skin. The pores of the core are substantially uniform while by comparison with the porous nature of the core, the skin is essentially non-porous. In fact, the skin has pores with diameters significantly smaller in size than those in the core.

Pore-forming agent

In either the thermoplastic or thermoset polymer composition, a pore-forming agent may be included to generate additional pores in the polymer matrix. The pore-forming agent is biocompatible, and soluble in body fluids and water as well as in the organic solvents. The pore-forming agent is further capable of diffusing or dispersing out of the coagulating polymer matrix and into the adjacent fluids, whereupon pores are generated in the polymer matrix.

The pore-forming agent, when combined with the thermoplastic polymer and solvent or with the thermoset polymer optionally containing a minimal amount of solvent, preferably forms a uniform mixture with the polymer either as a dispersion or suspension, or as a solution. When the mixture is administered to an implant site, the solvent and/or pore-forming agent preferably dissipate or diffuse into surrounding tissue fluids causing the formation of microporous channels within the coagulating polymer matrix. Optionally, the pore-forming agent may become incorporated into the polymer matrix, and dissipate into the surrounding tissue fluids

at a rate slower than that of the solvent, or be released from the matrix by biodegradation or bioerosion. The porous matrices formed through the inclusion of a pore-forming agent have a pore structure in which the pores are substantially similar in size throughout the matrix structure.

Preferably, the pore-forming agent is combined with the thermoplastic polymer and solvent, or the thermoset pre-polymer or copolymer mixture before the matrix is formed. The pore-forming agent may form a mixture solution or dispersion with the polymer.

Pore-forming agents include, any pharmaceutically acceptable organic or inorganic water-soluble substance that is substantially miscible in water and body fluids and will dissipate from the *in situ* formed matrix into body fluids. The pore-forming agent may also be a water-immiscible substance that rapidly degrades to a water-soluble substance. In the thermoplastic polymer composition of the invention, it is further preferred that the pore-forming agent is miscible or dispersible in the organic solvent to form a uniform mixture with the polymer moiety. Suitable pore-forming agents include, for example, sugars such as sucrose and dextrose, salts such as sodium chloride and sodium carbonate, and polymers such as hydroxylpropylcellulose, carboxymethylcellulose, polyethylene glycol, and polyvinylpyrrolidone.

The concentration of pore-forming agent relative to polymer in the composition will vary according to the degree of pore-formation desired. Generally, this concentration will range from 0.01g of pore-forming agent per gram of polymer to about 1g per gram.

The size or diameter of the pores formed in the matrix may be modified by the size and/or distribution of the pore-forming agent within the polymer matrix. For example, pore-forming agents which are relatively insoluble in the polymer mixture, may be selectively included in the composition according to particle size to generate pores having a diameter which corresponds to the size of the pore-forming agent. Pore-forming agents which are soluble in the polymer mixture may vary the pore size and porosity of the polymer matrix according to the pattern of distribution and/or aggregation within the mixture and resulting polymer matrix.

The concentration of water-soluble components, such as the solvent and/or pore-forming agent, in the composition may vary the porosity of the polymer matrix. For example, a composition having a high concentration of water-soluble substances may produce a polymer matrix having a high degree of porosity.

To provide an effective implant for bone cell regrowth and tissue regeneration, it is preferred that the diameter of the pores be about 3-500 microns, more preferably about 3-200 microns, and most preferably 75-150 microns. It is further preferred that the matrix has a porosity of about 5-95%, preferably about 25-85% in order to provide optimum cell and tissue ingrowth into the matrix and optimum structural integrity.

Pore diameter and distribution within the polymer matrix may be measured, as for example, according to scanning electron microscopy methods by examination of cross-sections of the polymer matrix. Porosity of the polymer matrix may be measured according to any suitable method, as for example, mercury intrusion porosimetry, specific gravity or density comparisons, calculation from scanning electronic microscopy photographs, and the like. Additionally, porosity may be calculated according to the proportion or percent of water-soluble material included in the polymer composition. For example, a composition which contains about 30% polymer and about 70% solvent and/or other water-soluble components will generate a polymer matrix having about 70% porosity.

Preferably, the pore-forming agent is dissipated immediately from the polymer matrix to generate a matrix having a porosity and pore structure effective to perform the particular purpose of the implant, as for example, a tissue regeneration site or a matrix for timed-release of a drug or medicament.

Implant for tissue regeneration

The composition may be administered to an implant site, as for example, whole tissue or tissue with a void such as a periodontal defect, a soft-tissue defect, a surgical incision, and the like. When the composition is administered to a tissue regeneration site, it is preferred that the implant provides a surface to facilitate the growth of regenerative tissue. For example, to enhance regeneration of hard tissue such as bone tissue, it is preferred that the polymer matrix will provide a support for new bone cell growth which will replace the matrix as it is gradually absorbed or eroded by body fluids.

The microporous polymer matrix is capable of biodegradation and/or bioabsorption within the implant site. According to the invention, the particular polymer and the molecular weight of the polymer may vary in the composition according to a desired duration or time interval of the degradation or bioerosion of the polymer matrix, as for example, a few weeks or several years. When the implant is used to enhance cell growth and tissue regeneration, it is preferred that the matrix disintegrate at a rate effective to allow replacement of the matrix by cell growth from the adjacent cells or tissue.

Biologically-active agent

The in situ formed implants may also provide a delivery system for biologically-active agents to adjacent or distant body tissues and organs. Biologically-active agents which may be used alone or in combination in the present compositions and implants include medicaments, drugs, or any suitable biologically-, physiologically- or pharmacologically-active substance which is capable of providing local or systemic biological or physiological activity in an animal, including a

human, and which is capable of being released from the polymer matrix into an adjacent or surrounding aqueous fluid.

5 The biologically-active agent may be miscible in the polymer and/or solvent to provide a homogenous mixture with the polymer, or insoluble in the polymer and/or solvent to form a suspension or dispersion with the polymer. It is highly preferred that the biologically-active agent be combined with the thermosetting polymer
10 composition almost immediately prior to administration of the composition to the implant site. It is further preferred that the bioactive agent will not contain functional groups which will interfere with the cross-linking reaction of the thermoset polymer. These conditions are readily determined by those of skill in the art simply by comparing the structure of the bioactive agent and the reacting moieties of the thermoset polymer.

Upon administration of the composition to the implant site, the biologically-active agent preferably becomes incorporated into the polymer matrix. As the matrix biodegrades and/or bioerodes, the biologically-active agent may be released from the matrix into the adjacent tissue fluids. Preferably, the biologically-active agent is released into the surrounding tissue fluids at a controlled rate. For example, the polymer matrix may be formulated to degrade after an effective and/or substantial amount of the biologically-active agent is released from the matrix. Release of a biologically-active agent having a low solubility in water, as for example a peptide or protein, may require the degradation of a substantial part of the polymer matrix to expose the agent directly to the surrounding tissue fluids. Thus, the release of the biologically-active agent from the matrix may be varied by, for example, the solubility of the biologically-active agent in water, the distribution of the biologically-active agent within the matrix, or the size, shape, porosity, solubility and biodegradability of the polymer matrix, among other factors.

40 The composition and in situ formed implant contain the biologically-active agent in an amount effective to provide a desired biological, physiological, pharmacological and/or therapeutic effect, optionally according to a desired release profile, and/or time duration of release. It is further preferred that the biologically-active agent is included in the polymer composition in an amount effective to provide an acceptable solution or dispersion viscosity.

45 In addition, the biologically-active agent may act as a pore-forming agent, or substance capable of generating pores in the polymer matrix of the implant. To enhance selective cell growth into the matrix, for example, it is preferred that the bioactive agent is released from the polymer matrix at a rate corresponding to that of cell migration and growth into newly formed pores of the matrix.

55 The biologically-active agent may also be a substance, or metabolic precursor thereof, which is capable of promoting growth and survival of cells and tissues, or

augmenting the activity of functioning cells, as for example, blood cells, neurons, muscle, bone marrow, bone cells and tissues, and the like. For example, the biologically-active agent may be a nerve growth promoting substance, as for example, a ganglioside, phosphatidylserine, a nerve growth factor, brain-derived neurotrophic factor, a fibroblast growth factor, and the like. In particular, the *in situ* implants are capable of enhancing regeneration of the periodontium by providing an outer surface having a porosity which serves as a physical barrier between an exposed root surface and encroaching epithelial cells to promote guided tissue regeneration.

To promote tissue growth, the biologically-active agent may be either a hard or soft tissue promoting substance or combinations thereof. Suitable tissue growth promoting agents include, for example, fibronectin (FN), endothelial cell growth factor (ECGF), cementum attachment extracts (CAE), human growth hormone (HGH), a Periodontal ligament cell growth factor, fibroblast growth factor (FGF), animal growth hormones, platelet derived growth factor (PDGF), epidermal growth factor (EGF), protein growth factor interleukin-1 (IL-1), transforming growth factor (TGF β -2), insulin-like growth factor II (IGF-II), human alpha thrombin (HAT), osteoinductive factor (OIF), bone morphogenetic protein (BMP) or protein derived therefrom, demineralized bone matrix, and releasing factors thereof.

Further, the agent may be a bone growth promoting substance such as hydroxyapatite, tricalcium phosphate, a di- or polyphosphonic acid, an anti-estrogen, a sodium fluoride preparation, a substance having a phosphate to calcium ratio similar to natural bone, and the like. A bone growth promoting substance may be in the form, as for example, of bone chips, bone crystals or mineral fractions of bone and/or teeth, a synthetic hydroxyapatite, or other suitable form. The agent may further be capable of treating metabolic bone disorders such as abnormal calcium and phosphate metabolism by, for example, inhibiting bone resorption, promoting bone mineralization, or inhibiting calcification.

See, for example, U.S. Patent No. 4,939,131 to Benedict et al., U.S. Patent No. 4,942,157 to Gall et al., U.S. Patent No. 4,894,373 to Young, U.S. Patent No. 4,904,478 to Walsdorf et al., and U.S. Patent No. 4,911,931 to Baylink, U.S. Patent No. 4,916,241 to Hayward et al., U.S. Patent No. 4,921,697 to Peterlik et al., U.S. Patent No. 4,902,296 to Bolander et al., U.S. Patent No. 4,294,753 to Urist, U.S. Patent No. 4,455,256 to Urist, U.S. Patent No. 4,526,909 to Urist, U.S. Patent No. 4,563,489 to Urist, U.S. Patent No. 4,596,574 to Urist, U.S. Patent No. 4,619,989 to Urist, U.S. Patent No. 4,761,471 to Urist, U.S. Patent No. 4,789,732 to Urist, U.S. Patent No. 4,795,804 to Urist, and U.S. Patent No. 4,857,456 to Urist.

Suitable biologically-active agents also include substances useful in preventing infection at the implant site, as for example, antiviral, antibacterial, antiparasitic,

antifungal substances and combinations thereof. The agent may further be a substance capable of acting as a stimulant, sedative, hypnotic, analgesic, anticonvulsant, and the like.

The delivery system can contain a large number of biologically-active agents either singly or in combination. Examples of these biologically-active agents include, but are not limited to:

- 5 Anti-inflammatory agents such as hydrocortisone, prednisone, fludrotisone, triamcinolone, dexamethasone, betamethasone and the like.
- 10 Anti-bacterial agents such as penicillins, cephalosporins, vancomycin, bacitracin, polymycins, tetracyclines, chloramphenicol, erythromycin, streptomycin, and the like.
- 15 Antiparasitic agents such as quinacrine, chloroquine, quinine, and the like.
- 20 Antifungal agents such as nystatin, gentamicin, miconazole, toltaftate, undecyclic acid and its salts, and the like.
- 25 Antiviral agents such as vidarabine, acyclovir, ribavirin, amantadine hydrochloride, iododeoxyuridine, dideoxyuridine, interferons and the like.
- 30 Antineoplastic agents such as methotrexate, 5-fluorouracil, bleomycin, tumor necrosis factor, tumor specific antibodies conjugated to toxins, and the like.
- 35 Analgesic agents such as salicylic acid, salicylate esters and salts, acetaminophen, ibuprofen, morphine, phenylbutazone, indomethacin, sulindac, tolmetin, zomepirac, and the like.
- 40 Local anaesthetics such as cocaine, benzocaine, novocaine, lidocaine, and the like.
- 45 Vaccines such as hepatitis, influenza, measles, mumps, rubella, hemophilus, diphtheria, tetanus, rabies, polio, and the like.
- 50 Central nervous system agents such as tranquilizers, sedatives, anti-depressants, hypnotics, B-adrenergic blocking agents, dopamine, and the like.
- 55 Growth factors such as colony stimulating factor, epidermal growth factor, erythropoietin, fibroblast growth factor, neural growth factor, human growth hormone, platelet derived growth factor, insulin-like growth factor, and the like.
- Hormones such as progesterone, estrogen, testosterone, follicle stimulating hormone, chorionic gonadotrophin, insulin, endorphins, somatotropins and the like.
- Antihistamines such as diphenhydramine, chlorphenamine, chlorcyclizine, promethazine, cimetidine, terfenadine, and the like.
- Cardiovascular agents such as verapamil hydrochloride, digitalis, streptokinase, nitroglycerine, papaverine, disopyramide phosphate, isosorbide dinitrate, and the like.
- Anti-ulcer agents such as cimetidine hydrochloride, isopropamide iodide, propantheline bromide, and

the like.

Bronchodilators such as metaproternal sulfate, aminophylline, albuterol, and the like.

Vasodilators such as theophylline, niacin, nicotinate esters, amylnitrate, minoxidil, diazoxide, nifedipine, and the like.

The biologically-active agent may be included in the compositions in the form of, for example, an uncharged molecule, a molecular complex, a salt, an ether, an ester, an amide, or other form to provide the effective biological or physiological activity.

Administration of the composition of the invention ultimately will be accomplished according to the wisdom and protocol of the patient's attending health care professional such as a physician, or if appropriate, a dentist. Choice of the particular composition will depend upon the malcondition or condition to be treated, which choice will be made by the attending health care professional. Application by syringe, or other means for applying a liquid to or into a tissue may be employed. Without a bioactive agent, the composition can function as a structure for promotion of cell growth and tissue repair. With a bioactive agent, the composition will not only function in such capacity but will also adopt the properties of the bioactive agent.

The amounts and concentrations of composition administered to the patient will generally be sufficient to accomplish the task intended. If that task is void space filling, enough composition will be administered to accomplish this task. For administration of bioactive agent, the amounts and release rates will follow recommendations of the manufacturer of the bioactive agent. Generally, the concentration of bioactive agent in the liquid polymer mixture will be from 0.01mg per g of mixture to 400mg per g of mixture.

Advantageously, the polymer compositions may be administered to an implant site, as for example, by injection with a syringe, whereupon the composition will solidify *in situ*. The resulting implant may thus be administered to an implant site without the need for surgical incision.

The invention will be described with reference to various specific and preferred embodiments and techniques.

EXAMPLE 1

A mixture comprising about 5% equimolar mixture of sodium carbonate and citric acid, about 34.8% poly(DL-lactide) (DL-PLA) and about 60.2% N-methyl pyrrolidone (NMP) was prepared by suspending sodium carbonate and citric acid in the polymer solution. The DL-PLA polymer had a molecular weight of about 30,000 daltons (inherent viscosity of 0.38 dL/g).

One drop of the mixture was precipitated into a vial containing phosphate-buffered saline (PBS) or water. The vial was placed in a 37°C shaker bath for about 48

hours. The sample was then removed from the bath, and dried *in vacuo* prior to examination by Scanning Electron Microscopy (SEM). The resulting article was porous with pores of about 5 μ in diameter, and a porosity of about 65%.

EXAMPLE 2

10 A mixture comprising about 5% sucrose, about 34.8% DL-PLA and about 60.2% NMP was prepared according to Example 1. A porous article was produced having pores of about 3 μ in diameter and a porosity of about 65%.

EXAMPLE 3

15 A mixture comprising about 5% poly(vinyl pyrrolidone)(PVP), about 34.8% DL-PLA and about 60.2% NMP was prepared according to Example 1. A porous article was produced having pores of about 5-10 μ in diameter and a porosity of about 65%.

EXAMPLE 4

20 25 A mixture comprising about 10% PVP, about 33.0% DL-PLA, and about 57.0% NMP was prepared according to Example 1. A porous article was produced having pores of about 5-20 μ in diameter and a porosity of about 65%.

EXAMPLE 5

30 35 In this example, a mixture was prepared comprising about 50% of two different molecular weights of DL-PLA and about 50% NMP. A water-soluble, low molecular weight DL-PLA (molecular weight of about 2000 daltons) was mixed with a higher molecular weight DL-PLA with an inherent viscosity of 0.38 dL/g (molecular weight of about 30,000 daltons). The DL-PLA mixture was dissolved in NMP to provide a mixture comprised of about 40 45 50 55 38% low molecular weight DL-PLA, about 12% higher molecular weight DL-PLA, and about 50% NMP. This mixture was then precipitated, incubated and dried according to Example 1. A porous article was produced having pores of about 10-50 μ in diameter, and about 50% porosity.

EXAMPLE 6

50 A mixture comprising about 5% ethoxydihydrosanguinarine (SaOEt), 27.5% DL-PLA and 67.5% NMP was prepared according to Example 1. SaOEt is an antimicrobial agent derivable from benzophenanthridine alkaloids. A porous article was produced having pores of about 15-30 μ in diameter and about 70% porosity.

EXAMPLE 7

A mixture comprising about 5% SaOEt, 27.5% DL-PLA and 67.5% NMP was prepared according to Example 1, the DL-PLA component having a molecular weight of about 10,000 daltons. A porous article was produced having pores of about 4-8 μ in diameter. A wet sample of the article was examined by X-ray tomography by scanning at intervals of about 0.25 mm. The articles showed porosity throughout with about 70% porosity.

EXAMPLE 8

An implant comprising about 5.0% sanguinarine chloride (SaCl), about 47.5% DL-PLA, and about 47.5% NMP was administered to a periodontal pocket of a human patient. SaCl is an antimicrobial and anti-inflammatory agent derivable from benzophenanthridine alkaloids. After 28 days, the implant was removed, dried *in vacuo* and examined by SEM. Pores having a diameter of about 1.2 μ and of about 10-20 μ were detected. Approximately 50% of the pores were 10-20 μ . The implant had a total porosity of about 50%.

EXAMPLE 9

A mixture comprising about 33% PVP, about 33% 50/50 copolymer of DL-lactide and glycolide (DL-PLG), and about 34% NMP was prepared according to Example 1. A porous article was produced having pores of about 3-10 μ . Examination of the article showed that the pores were arranged in an interconnecting network. The article had a porosity of about 65%.

EXAMPLE 10

A lyophilized sample of fibronectin, a tissue growth and cell attachment factor, was added to a solution of DL-PLA in NMP to provide a dispersion comprising about 13.2% wt-% lyophilized fibronectin, about 30.4 wt-% DL-PLA, and about 56.4 wt-% NMP. As a result of the lyophilization process, the lyophilized fibronectin contained various salts with only about 0.89% active component. This dispersion was added to a phosphate-buffered receiving solution wherein it coagulated into a solid matrix. The receiving solution was maintained at 37°C under agitation and changed periodically to preclude a high concentration of fibronectin within the receiving solution. The receiving solution was analyzed for total protein concentration by the Pierce BCA protein assay. The cumulative percentage of fibronectin released from the matrix was calculated. About 12% of the fibronectin component was released after one day, about 25% after 2 days, about 26% after 3 days, about 28% after 4 days, 30% after 5 days, and 33% after 7 days. The porosity of the solid matrix of the implant was initially about 55%. The porosity level of the matrix

increased as the fibronectin component was released over time. The pores of greater than 3 μ in diameter were produced by the dissolving fibronectin component.

EXAMPLE 11

Norethindrone and ethinylestradiol, birth control agents, may be added to a solution of DL-PLA in NMP to provide a liquid mixture containing about 10% wt-% norethindrone, about 1 wt-% ethinylestradiol, about 33 wt-% DL-PLA and about 56 wt-% NMP. The mixture can then be injected under the skin of an animal where it coagulates to form a solid microporous implant. Levels of norethindrone and ethinylestradiol in the blood can be measured over time. The effect on rates of pregnancy can also be measured. The implant advantageously functions to release birth control agents continuously over time and does not have to be removed by surgery.

EXAMPLE 12

Terfenadine, an antiallergy medication, may be added to a solution of DL-PLA in NMP to provide a liquid mixture containing about 10 wt-% terfenadine, about 33 wt-% DL-PLA and 57 wt-% NMP. The mixture can then be injected under the skin of an animal where it coagulates to form a solid microporous implant. The level of terfenadine in the blood can be measured over time. The efficacy of the implant in controlling allergy symptoms can also be measured.

EXAMPLE 13

Bone chips and bone morphogenetic protein can be added to form a liquid mixture containing about 10 wt-% bone chips, about 1 wt-% bone morphogenetic protein, about 5 wt-% PVP, about 33 wt-% DL-PLA, and about 51 wt-% NMP. The mixture can then be injected to fill in a bone defect in a crushed cheekbone. The mixture coagulates *in situ*, conforming to the shape of the site, and filling in the damaged tissue. Healing and regeneration of bone tissue can be monitored over time.

EXAMPLE 14

Ovine follicle stimulating hormone, an ovulation stimulatory agent, may be added to form a liquid mixture containing about 2 wt-% ovine follicle stimulating hormone, about 41 wt-% DL-PLA, and about 57 wt-% NMP. The solution can be injected subdermally into a cow to form a solid microporous implant. The ovulation rate can be measured 4-6 days after oestrus.

55 Claims

1. A composition suitable for forming an *in situ* solid implant in an animal, comprising: a formulation of a

biodegradable, bioerodible thermoplastic polymer that is insoluble in aqueous or body fluid, and an organic solvent that is miscible, soluble or dispersible in aqueous or body fluid; the composition being capable of coagulating or solidifying to form a solid or gelatinous microporous matrix upon its contact with aqueous or body fluid; the matrix being a core surrounded by a skin, the core containing pores of diameters from 10 to 1000 microns, and the skin containing pores of smaller diameters than those of the core pores.

2. A composition suitable for forming an *in situ* solid implant in an animal, comprising: a formulation of a biodegradable, bioerodible thermoset polymer; the composition being capable of forming a solid or gelatinous microporous matrix which is a core surrounded by a skin, the core containing pores of diameters from 10 to 1000 microns, and the skin containing pores of smaller diameters than those of the core pores.
3. A composition according to claim 2, wherein the polymer is an acrylic ester-terminated biodegradable prepolymer capable of cross-linking to form a polymer matrix.
4. A composition according to claim 2, further comprising a curing agent.
5. A composition according to claim 2, further comprising a pore-forming agent or an organic solvent that is miscible, soluble or dispersible in aqueous or body fluid, or combination thereof.
6. A composition according to claims 1 or 2, wherein the skin pores are of a size such that the skin is functionally non-porous in comparison with the core.
7. A composition according to claim 1, further comprising a pore-forming agent.
8. A composition according to claims 5 or 7, wherein the pore-forming agent is a sugar, salt, or water-soluble polymer, or water-insoluble substance that degrades to a water soluble substance.
9. A composition according to claims 1 or 3, wherein the polymer or prepolymer is selected from the group consisting of polylactides, polyglycolides, polycaprolactones, polyanhydrides, polyamides, polyurethanes, polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates, polyphosphazenes, polyhydroxybutyrate, polyhydroxyvalerate, polyalkylene oxalates, polyalkylene succinates, poly(amino acids), poly(methyl vinyl ether), and

copolymers, terpolymers, and any combination thereof.

- 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120 125 130 135 140 145 150 155 160 165 170 175 180 185 190 195 200 205 210 215 220 225 230 235 240 245 250 255 260 265 270 275 280 285 290 295 300 305 310 315 320 325 330 335 340 345 350 355 360 365 370 375 380 385 390 395 400 405 410 415 420 425 430 435 440 445 450 455 460 465 470 475 480 485 490 495 500 505 510 515 520 525 530 535 540 545 550 555 560 565 570 575 580 585 590 595 600 605 610 615 620 625 630 635 640 645 650 655 660 665 670 675 680 685 690 695 700 705 710 715 720 725 730 735 740 745 750 755 760 765 770 775 780 785 790 795 800 805 810 815 820 825 830 835 840 845 850 855 860 865 870 875 880 885 890 895 900 905 910 915 920 925 930 935 940 945 950 955 960 965 970 975 980 985 990 995 1000 1005 1010 1015 1020 1025 1030 1035 1040 1045 1050 1055 1060 1065 1070 1075 1080 1085 1090 1095 1100 1105 1110 1115 1120 1125 1130 1135 1140 1145 1150 1155 1160 1165 1170 1175 1180 1185 1190 1195 1200 1205 1210 1215 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- wässriger Flüssigkeit oder Körperflüssigkeit unlöslich ist, und eines organischen Lösemittels, das in einer wässrigen Flüssigkeit oder Körperflüssigkeit löslich oder dispergierbar oder damit mischbar ist; wobei die Zusammensetzung zur Koagulation oder Verfestigung unter Bildung einer festen oder gelatinösen mikroporösen Matrix beim Kontakt mit der wässrigen Flüssigkeit oder Körperflüssigkeit in der Lage ist; wobei die Matrix ein von einer Haut umgebener Kern ist, der Kern Poren mit einem Durchmesser von 10 bis 1000 µm enthält und die Haut Poren mit kleineren Durchmessern als jene der Kernporen enthält.
2. Zusammensetzung, die zum Bilden eines festen *in situ* - Implantats in einem Tier geeignet ist, umfassend: eine Formulierung eines bioabbaubaren, bioerodierbaren, wärmehärtbaren Polymeren; wobei die Zusammensetzung zur Bildung einer festen oder gelatinösen mikroporösen Matrix, welche ein von einer Haut umgebener Kern ist, in der Lage ist, wobei der Kern Poren mit Durchmessern von 10 bis 1000 µm enthält und die Haut Poren mit kleineren Durchmessern als jene der Kernporen enthält.
3. Zusammensetzung gemäß Anspruch 2, worin das Polymer ein bioabbaubares, mit Acrylsäureester terminiertes Präpolymer ist, welches zur Vernetzung unter Bildung einer Polymermatrix in der Lage ist.
4. Zusammensetzung gemäß Anspruch 2, ferner ein Härtungsmittel umfassend.
5. Zusammensetzung gemäß Anspruch 2, welches ferner ein porenbildendes Mittel oder ein organisches Lösemittel umfaßt, welches in wässriger Flüssigkeit oder Körperflüssigkeit, oder einer Kombination davon, löslich oder dispergierbar oder damit mischbar ist.
6. Zusammensetzung gemäß Anspruch 1 oder 2, worin die Hautporen eine solche Größe aufweisen, daß die Haut funktionell im Vergleich zu dem Kern nicht porös ist.
7. Zusammensetzung gemäß Anspruch 1, ferner ein porenbildendes Mittel enthaltend.
8. Zusammensetzung gemäß Anspruch 5 oder 7, worin das porenbildende Mittel Zucker, Salz oder wasserlösliches Polymer oder in Wasser unlösliche Substanz ist, welche zu einer wasserlöslichen Substanz zerfällt.
9. Zusammensetzung gemäß Anspruch 1 oder 3, worin das Polymer oder Präpolymer gewählt wird aus der Polylactide, Polyglycolide, Polycaprolac-
- 5 tone, Polyanhydride, Polyamide, Polyurethane, Polyesteramide, Polyorthoester, Polydioxanone, Polyacetale, Polyketale, Polycarbonate, Polyorthocarbonat, Polyphosphazene, Polyhydroxybutyrate, Polyhydroxyvalerate, Polyalkylenoxalate, Polyalkylsuccinate, Poly(aminosäuren), Poly(methylvinylether) und Copolymere, Terpolymere und jedwede Kombination davon umfassenden Gruppe.
10. Zusammensetzung gemäß Anspruch 1 oder 5, wobei das Lösemittel gewählt wird aus der N-Methyl-2-pyrrolidon, 2-Pyrrolidon, Ethanol, Propylenglykol, Propylencarbonat, Aceton, Essigsäure, Ethylacetat, Ethyllactat, Methylacetat, Methylethylketon, Dimethylformamid, Dimethylsulfoxid, Dimethylsulfon, Tetrahydrofuran, Caprolactam, Decylmethylsulfoxid, Ölsaure, N,N-Diethyl-m-toluamid, 1-Dodecylazacycloheptan-2-on und jedwede Kombination davon umfassenden Gruppe.
- 15 11. Zusammensetzung gemäß 1 oder 2, ferner umfassend mindestens ein biologisch aktives Mittel, wobei das biologisch aktive Mittel, welches mit dem wärmehärtbaren Polymer kombiniert wird, frei an funktionellen Gruppen ist, welche bei der Wärmehärtungsreaktion des wärmehärtbaren Polymeren stören könnten.
- 20 12. Zusammensetzung gemäß Anspruch 11, worin das biologisch aktive Mittel ein Polypeptid oder Derivat davon ist, abgeleitet von einer natürlichen, synthetischen oder rekombinanten DNA-Quelle.
- 25 13. Zusammensetzung gemäß Anspruch 11, worin das biologisch aktive Mittel gewählt wird aus der entzündungshemmende Mittel, antibakterielle Mittel, antiparasitische Mittel, antifungale Mittel, antivirale Mittel, antineoplastische Mittel, analgetische Mittel, Anästhetika, Impfstoffe, Mittel für das zentrale Nervensystem, Wachstumsfaktoren, Hormone, Antihistamine, die Knochenbildung induzierende Mittel, kardiovaskuläre Mittel, Mittel gegen Geschwüre, Bronchodilatoren, Vasodilatoren, Mittel zur Geburtenkontrolle und die Fruchtbarkeit erhöhende Mittel umfassenden Gruppe.
- 30 14. Zusammensetzung gemäß Anspruch 11, worin das biologisch aktive Mittel in der Lage ist, die biologische oder physiologische Aktion des reproduktiven Systems zu verändern.
- 35 15. Verwendung einer Zusammensetzung gemäß einem oder mehreren der Ansprüche 1 bis 14 zur Herstellung einer Präparation zur *in situ*-Bildung eines mikroporösen bioabbaubaren Implantats in einem Körper.
- 40 16. Zusammensetzung gemäß einem oder mehreren
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der Ansprüche 1 bis 14 zur Verwendung als ein sich in situ bildendes, mikroporöses, bioabbaubares Implantat in einem Körper.

Revendications

1. Composition convenant à la formation d'un implant solide in situ dans un animal, comprenant une formulation d'un polymère thermoplastique bio-érodable, biodégradable, qui est insoluble dans les fluides aqueux ou corporels, et un solvant organique qui est miscible, soluble ou dispersible dans un fluide aqueux ou corporel ; la composition pouvant se coaguler ou se solidifier pour former une matrice microporeuse solide ou gélantineuse après contact avec un fluide aqueux ou corporel ; la matrice étant un cœur entouré d'une peau, le cœur contenant des pores ayant un diamètre de 10 à 1000 micromètres, et la peau contenant des pores ayant un diamètre plus petit que celui des pores du cœur.
2. Composition permettant de former un implant solide in situ dans un animal, comprenant une formulation d'un polymère thermodurcissable bio-érodable et biodégradable ; la composition étant à même de former une matrice microporeuse solide ou gélantineuse, qui est un cœur entouré d'une peau, le cœur contenant des pores ayant un diamètre de 10 à 1000 micromètres, et la peau contenant des pores ayant un diamètre plus petit que celui des pores du cœur.
3. Composition selon la revendication 2, dans laquelle le polymère est un prépolymère biodégradable à terminaison acrylate pouvant se réticuler pour former une matrice polymère.
4. Composition selon la revendication 2, qui comprend en outre un agent de durcissement.
5. Composition selon la revendication 2, qui comprend en outre un agent porogène ou un solvant organique qui est miscible, soluble ou dispersible dans un fluide aqueux ou corporel, ou une de leurs combinaisons.
6. Composition selon la revendication 1 ou 2, dans laquelle les pores de la peau ont une taille telle que la peau soit fonctionnellement non-poreuse par comparaison avec le cœur.
7. Composition selon la revendication 1, qui comprend en outre un agent porogène.
8. Composition selon les revendications 5 ou 7, dans laquelle l'agent porogène est un sucre, un sel ou un polymère soluble dans l'eau, ou une substance insoluble dans l'eau qui se dégrade pour donner

une substance soluble dans l'eau.

9. Composition selon les revendications 1 ou 3, dans laquelle le polymère ou prépolymère est choisi dans le groupe comprenant les polylactides, les polyglycolides, les polycaprolactones, les polyanhydrides, les polyamides, les polyuréthannes, les polyesteramides, les polyorthoesters, les polydioxannones, les polyacétals, les polycétals, les polycarbonates, les polyorthocarbonates, les polyphosphazènes, les polyhydroxybutyrate, les polyhydroxylalérates, les poly(oxalates d'alkylène), les poly(succinates d'alkylène), les poly(acides aminés), le poly(méthylvinyléther) et leurs copolymères et terpolymères et toutes combinaisons d'entre eux.
10. Composition selon les revendications 1 ou 5, dans laquelle le solvant est choisi dans le groupe comprenant la N-méthyl-2-pyrrolidone, la 2-pyrrolidone, l'éthanol, le propyléneglycol, le carbonate de propylène, l'acétone, l'acide acétique, l'acétate d'éthyle, le lactate d'éthyle, l'acétate de méthyle, la méthyléthylcétone, le diméthylformamide, le diméthylsulfoxyde, la diméthylsulfone, le tétrahydrofurane, le caprolactame, le décylméthylsulfoxyde, l'acide oléique, le N,N-diéthyl-m-toluamide, la 1-dodécylazacycloheptane-2-one et l'une quelconque de leurs combinaisons.
11. Composition selon les revendications 1 ou 2, qui comprend en outre au moins un agent ayant une activité biologique, où l'agent ayant une activité biologique qui est combiné au polymère thermodurcissable est exempt de groupes fonctionnels qui risqueraient d'interférer avec la réaction de thermodurcissement du polymère thermodurcissable.
12. Composition selon la revendication 11, dans laquelle l'agent ayant une activité biologique est un polypeptide ou ses dérivés, qui dérivent d'une source d'ADN naturel, synthétique ou recombinant.
13. Composition selon la revendication 11, dans laquelle l'agent ayant une activité biologique est choisi dans le groupe comprenant les agents anti-inflammatoires, les agents antibactériens, les agents antiparasitaires, les agents antifongiques, les agents antiviraux, les agents antinéoplasiques, les agents analgésiques, les anesthésiques, les vaccins, les agents qui agissent sur le système nerveux central, les facteurs de croissance, les hormones, les antihistaminiques, les agents ostéoinducteurs, les agents cardiovasculaires, les agents anti-ulcérateurs, les bronchodilatateurs, les vasodilatateurs, les agents de régulation des naissances et les agents renforçant la fertilité.

14. Composition selon la revendication 11, dans laquelle l'agent ayant une activité biologique est à même de modifier l'action biologique ou physiologique du système de reproduction.

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15. Utilisation d'une composition selon l'une ou plusieurs des revendications 1 à 14 pour la fabrication d'une préparation pour formation in situ d'un implant biodégradable microporeux dans un organisme.

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16. Composition selon l'une ou plusieurs des revendications 1 à 14 pour utilisation en tant qu'implant biodégradable microporeux à formation in situ dans un organisme.

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